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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,841	10/20/2005	Bradley T Hyman	M0765.70061US00	7670

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,841	HYMAN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *4,7,8,13,16,17 and 19-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9-12,14,15 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal matters

The response filed on 15 December 2008 has been received and entered in full. Claims 1-28 are pending.

Claims 4, 7, 8, 13, 16, 17 and 19-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11 June 2008.

Claims 1-3, 5, 6, 9-12, 14, 15 and 18 are under examination in the instant office [action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, 6, 9-12, 14, 15 and 18 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,156,311 to Strickland et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are directed to a method for reducing catabolism of extracellular secreted amyloid β-precursor protein which comprises contacting a mammalian cell with an agent that reduces the amount or rate of binding of amyloid β-precursor protein (APP) with the low density lipoprotein receptor-related protein (LRP). Thus, the instant claims and the patented claims are obvious variants, since the low density lipoprotein receptor-related

protein (as in the patent) is in the same receptor family as the very low density lipoprotein receptor (as in the instant claims).

Claims 1-3, 5, 6, 9-12, 14, 15 and 18 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,447,775 to Strickland et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are directed to a method for reducing catabolism of full length amyloid β-precursor protein which comprises contacting a mammalian cell with an agent that selectively reduces the amount or rate of binding of full length APP with the LRP. Thus, the instant claims and the patented claims are obvious variants, since the low density lipoprotein receptor-related protein (as in the patent) is in the same receptor family as the very low density lipoprotein receptor (as in the instant claims).

In the reply filed on 15 December 2008, applicants assert that lipoprotein receptor-related protein and very low density lipoprotein receptor are not "obvious variants" of one another. Applicants assert that the LDL receptor (LDL-R) family consists of at least four members, LRP, VLDL-R, LDL-R, and glycoprotein 330 (U.S. Patent No. 6,156,311) that have dissimilar properties and functions. Applicants assert that Willnow et al. (J Biol Chem 267:26172-26180 (1992)), cited in Strickland et al., teach that LRP "is much larger than LDL receptor (4525 versus 839 amino acids)" and that "LRP does not bind LDL, but it does bind beta-migrating very low density lipoproteins (beta-VLDL)" demonstrating that LRP and LDL-R diverge not only

structurally but also functionally. Applicants assert that this example of divergent structural and functional characteristics of LRP and LDL-R demonstrates that members in the LDL receptor family (i.e., the "same receptor family") are not "obvious variants" of one another. Applicants assert that LRP is also structurally very dissimilar to VLDL-R; these two amino acid sequences share an overall identity of only 7.2%, LRP being much larger than VLDL-R. Applicants assert that it is well known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties, including binding to other proteins or other molecules. Applicants assert that Kaye et al. (Exhibit B), teach that a single amino acid substitution results in a protein defective, inter alia, in binding to a specific protein. Applicants assert that Kaye et al. state that "[w]e have now demonstrated.., that a single point mutation.., is sufficient to generate an RB 1 defective in phosphorylation and oncoprotein binding". Applicants assert that it is thus evident from Kaye et al. that amino sequence is essential for protein function, including protein binding.

Applicants' arguments have been fully considered and are not found persuasive. Strickland explicitly states "it is an object of the present invention to provide agents which bind to APP or LDL-receptor family members and reduce the interaction, cellular internalization, and subsequent catabolism of APP" (Emphasis added; col.3, lines 11-14) and teaches that the VLDL-R receptor is in the same receptor family as LRP, i.e. the LDL-receptor family (col.2, lines 20-25). Strickland's abstract states, "The present invention broadly relates to the treatment, diagnosis, and prophylactic prevention of Alzheimer's disease. More specifically, the present invention relates to methods and

compositions for preventing the endocytosis and cellular internalization of integral membrane amyloid β-precursor protein (APP) and its subsequent catabolism by blocking or interfering with the association or binding of APP with members of the low density lipoprotein receptor family." (Emphasis added). These explicit teachings demonstrate that the strength of the *prima facie* obviousness showing outweighs applicants' assertions that the receptors do not share significant homology or may have at least one function that is not shared. Thus, applicants' assertions that upon reading the Strickland et al. patent a person of ordinary skill in the art would not have been motivated to search for additional LDL receptor family members that may interact with APP because there is no teaching or suggestion in this reference that additional LDL receptor family members, apart from LRP, would be able to interact with APP, or that it would be desirable or necessary to look for interactions of APP with additional LDL-R family members is inaccurate. Contrary to applicants' assertions, Strickland's explicit teachings set forth above indeed suggest that additional LDL receptor family members, apart from LRP, would be able to interact with APP VLDL-R and therefore it would indeed be desirable to practice the claimed methods with additional LDL-R family members, e.g. VLDL-R.

The instant finding of obviousness can also be considered analogous to the "obvious to try" rationale, which involves choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success (see MPEP §2144.3). Here, as applicants have pointed out Strickland teaches that the LDL receptor (LDL-R) family consists of at least four members, LRP, VLDL-R, LDL-R, and glycoprotein 330.

Given Strickland's explicit teachings that it is an object of the invention to provide agents which bind to APP or LDL-receptor family members and reduce the interaction, cellular internalization, and subsequent catabolism of APP by blocking or interfering with the association or binding of APP with members of the low density lipoprotein receptor family and given the limited number of number of family members listed in the patent, i.e. 4, it would have been obvious to try the claimed methods. Strickland explicitly supports the predictability that agents which bind to either APP or to LDL-receptor family members would reduce the interaction, cellular internalization, and subsequent catabolism of APP because such agents would be capable of interfering with the association of APP with the LDL-receptor family members, such as VLDL-R. Hence, Strickland supports a reasonable expectation of success. Regardless of whether these receptor family members are dissimilar or have allegedly different functions, Strickland teaches that they have at least that one common function, binding of APP and catabolism of APP and interfering with such would be useful in the treatment, diagnosis and prevention of Alzheimer's disease.

Additionally, it is noted that some of the issued claims are not just obvious variants of the pending claims; in some cases they **anticipate** the pending claims. For example, the instant dependent claims 2 and 11 require that the claimed agent is one which binds to amyloid precursor protein and dependent claims 3 and 12 require that the agent is an antibody or an antibody fragment containing the antigen binding domain that binds to amyloid precursor protein. These limitations are anticipated by claims 2 and 4 of the '311 patent and are anticipated by claims 3 and 4 of the '775 patent. In

each case claims are drawn to methods of reducing catabolism of Abeta by contacting with anti-APP antibody. Thus, the issued claims anticipate the pending claims. Whether or not they are obvious variants is immaterial when the question is one of anticipation. See MPEP 804(II)(B)(I).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 6, 9-12, 14, 15 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,156,311 to Strickland et al. (cited previously).

The claims are directed to a method for reducing catabolism of extracellular secreted amyloid precursor protein comprising contacting a mammalian cell with an agent that reduces the amount or rate of binding of amyloid precursor protein (APP) with the very low density lipoprotein receptor (VLDL-R).

The Strickland et al. patent teaches a method for reducing catabolism of extracellular secreted amyloid β-precursor protein which comprises contacting a mammalian cell with an agent that reduces the amount or rate of binding of amyloid β-precursor protein with the low density lipoprotein receptor-related protein (see patented claim 1), as in the instant claim 1. The patent teaches that the agent can be one that binds to APP or one that binds to LRP (see patented claims 2 and 3), as in the instant claims 2 and 11. The patent teaches that the agent can be an antibody or fragment thereof that binds to APP or LRP (see patented claims 3 and 4), as in the instant claims 3 and 12. The patent teaches that the contacting occurs *in vitro* (see patented claim 6), as in the instant claim 9. The patent teaches methods for reducing the rate of onset or the severity of Alzheimer's disease, comprising administering to an animal, such as a human, one or more Group I agents (agents which bind to the APP-binding site on the LRP particle) and/or one or more Group II agents (agents which bind to the LRP-binding

site found on APP) in an amount effective to reduce the rate of APP attachment to its receptor (col.3, lines 23-26 and col.4, lines 16-21), as in the instant claims 10 and 18.

The difference between the methods disclosed in the Strickland et al. patent and those of the claimed invention is that said patent does not explicitly teach that the Group I agents include those that bind to the APP-binding site on the VLDL-R. However, upon reading the disclosure of the Strickland et al. patent, the skilled artisan would have recognized the desirability of developing additional methods of reducing the catabolism of APP and of treating Alzheimer's disease. Furthermore, the patent teaches, "it is an object of the present invention to provide agents which bind to APP or LDL-receptor family members and reduce the interaction, cellular internalization, and subsequent catabolism of APP" (col.3, lines 11-14) and teaches that the VLDL-R receptor is in the same receptor family as LRP, i.e. the LDL-receptor family (col.2, lines 20-25).

As evidenced by the prior art, the skilled artisan would have known that developing additional methods to decrease the catabolism of APP would be desirable. Furthermore, it would have been reasonable to predict that that an agent that binds to the APP-binding site of VLDL-R (including an antibody or fragment thereof) could be successfully used as an alternative method of reducing APP catabolism to treat Alzheimer's disease, as in claims 5, 6, 14 and 15. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to improve Strickland et al.'s methods of reducing APP catabolism to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her

technical grasp to obtain predictable results. Such would amount to substitution of one known equivalent for another, i.e. VLDL-R for LRP.

Applicants assert that lipoprotein receptor-related protein (LRP) and very low density lipoprotein receptor (VLDL-R) are not "known equivalents" of one another. Applicants assert that the prior art teaches that the LDL receptor (LDL-R) family consists of at least four members, LRP, VLDL-R, LDL-R, and glycoprotein 330 (gp330) that have dissimilar properties and functions. Applicants assert that Willnow et al., cited in Strickland et al., present data that suggest that LRP and LDL-R diverge structurally and functionally. Applicants assert that LRP and VLDL-R share an overall sequence identity of only 7.2%. Thus, applicants assert that one of ordinary skill in the art would not consider LRP and VLDL-R "known equivalents" of one another. Applicants assert that upon reading the Strickland et al. patent a person of ordinary skill in the art would not have been motivated to search for additional LDL receptor family members that may interact with APP because there is no teaching or suggestion in this reference that additional LDL receptor family members, apart from LRP, would be able to interact with APP, or that it would be desirable or necessary to look for interactions of APP with additional LDL-R family members and to improve Strickland et al.'s methods. Applicants assert that given the very low overall sequence homology of LRP and VLDL-R and without a priori knowledge of the VLDL-R/APP interaction, a person of ordinary skill in the art would not have had any reason to determine if VLDL-R binds to APP, and would not have had a reasonable expectation of success of finding that VLDL-R would

be likely to bind to APP. Applicants assert that in view of the prior art, as a whole, it was a surprising result, obtained by applicants, that VLDL-R also binds to APP and mediates APP endocytosis similar to LRP. Hence, applicants assert that it was unexpected that VLDL-R represents a viable target for reducing catabolism of extracellular secreted APP by disrupting the interaction of APP and VLDL-R, as instantly claimed.

Applicants' arguments have been fully considered and are not found persuasive. As set forth above, Strickland explicitly states "it is an object of the present invention to provide agents which bind to APP or LDL-receptor family members and reduce the interaction, cellular internalization, and subsequent catabolism of APP" (Emphasis added; col.3, lines 11-14) and teaches that the VLDL-R receptor is in the same receptor family as LRP, i.e. the LDL-receptor family (col.2, lines 20-25). Strickland's abstract states, "The present invention broadly relates to the treatment, diagnosis, and prophylactic prevention of Alzheimer's disease. More specifically, the present invention relates to methods and compositions for preventing the endocytosis and cellular internalization of integral membrane amyloid β-precursor protein (APP) and its subsequent catabolism by blocking or interfering with the association or binding of APP with members of the low density lipoprotein receptor family." (Emphasis added). These explicit teachings demonstrate that the strength of the *prima facie* obviousness showing outweighs applicants' assertions that the receptors do not share significant homology or may have at least one function that is not shared. Thus, applicants' assertions that upon reading the Strickland et al. patent a person of ordinary skill in the art would not have been motivated to search for additional LDL receptor family members that may

interact with APP because there is no teaching or suggestion in this reference that additional LDL receptor family members, apart from LRP, would be able to interact with APP, or that it would be desirable or necessary to look for interactions of APP with additional LDL-R family members is inaccurate. Contrary to applicants' assertions, Strickland's explicit teachings set forth above indeed suggest that additional LDL receptor family members, apart from LRP, would be able to interact with APP VLDL-R and therefore it would indeed be desirable to practice the claimed methods with additional LDL-R family members, e.g. VLDL-R.

The instant finding of obviousness can also be considered analogous to the "obvious to try" rationale, which involves choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success (see MPEP §2144.3). Here, as applicants have pointed out Strickland teaches that the LDL receptor (LDL-R) family consists of at least four members, LRP, VLDL-R, LDL-R, and glycoprotein 330. Given Strickland's explicit teachings that it is an object of the invention to provide agents which bind to APP or LDL-receptor family members and reduce the interaction, cellular internalization, and subsequent catabolism of APP by blocking or interfering with the association or binding of APP with members of the low density lipoprotein receptor family and given the limited number of number of family members listed in the patent, i.e. 4, it would have been obvious to try the claimed methods. Strickland explicitly supports the predictability that agents which bind to either APP or to LDL-receptor family members would reduce the interaction, cellular internalization, and subsequent catabolism of APP because such agents would be capable of interfering with the

association of APP with the LDL-receptor family members, such as VLDL-R. Hence, Strickland supports a reasonable expectation of success. Regardless of whether these receptor family members are dissimilar or have allegedly different functions, Strickland teaches that they have at least that one common function, binding of APP and catabolism of APP and interfering with such would be useful in the treatment, diagnosis and prevention of Alzheimer's disease.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch, Ph.D.
Patent Examiner
Art Unit 1649
12 April 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
April 13, 2009